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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,978	01/09/2001	Eugene Roussel	210582.0001/1US	6809

8933 7590 07/30/2003

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EXAMINER	
YU, MISOOK	
ART UNIT	**PAPER NUMBER**
1642	24

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Interview Summary	Application No.	Applicant(s)	
	09/756,978	ROUSSEL, EUGENE	
	Examin r	Art Unit	
	MISOOK YU, Ph.D.	1642	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MISOOK YU, Ph.D.*.

(3)*Dr. Gary Colby* .

(2) *Dr. Anthony Caputa*.

(4)*Dr. Eugene Rousal*.

Date of Interview: *29 July 2003*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☒ Yes e)☐ No.
If Yes, brief description: *Draft Response*.

Claim(s) discussed: *1-66*.

Identification of prior art discussed: *Lee et al (2000) and Tannenbaum et al (1998)*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Discussed why the claims are not obvious and applicant would provide arguments to obviate the rejection of record*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

Examiner's signature, if required

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)
In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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FACSIMILE TRANSMITTAL SHEET

TO:	Examiner Yu
FIRM/COMPANY:	United States Patent and Trademark Office **Serial No. 09/756,978**
FACSIMILE NUMBER:	703.746.7647
CONFIRMATION TELEPHONE:	703.308.2454
FROM:	Gary D. Colby
DIRECT DIAL:	215.979.1849
DATE:	July 25, 2003
USER NUMBER:	0306
FILE NUMBER:	E0631-00001
TOTAL # OF PAGES: (INCLUDING COVERSHEET)	10
MESSAGE:	***DRAFT* Response and Request for Reconsideration attached.** **NOT FOR ENTRY**

NOTE: Original will not follow

If there is a problem with this transmission, please call us as soon as possible at 215.979.1021.

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Not For Entry

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Appln. of:	Eugene Roussel	Group Art Unit:	1642
Serial No.:	09/756,978	Conf. No.:	6809
Filed:	9 January 2001	Examiner:	Misook Yu
For:	Therapeutic Modulation of the Tumor Inflammatory Response	Atty Docket No.:	E0631-00001

DRAFT

RESPONSE AND REQUEST FOR RECONSIDERATION

Introductory Comments

This paper is filed in response to the Office Action mailed 11 April 2003 (Paper No. 22). Please consider the following remarks. This response is timely filed in view of the enclosed Petition for a one-month extension of time which extends the time for response up to and including 11 August 2003.

The Applicant appreciates the Examiners' agreement to participate in a telephone interview scheduled for **29 July 2003 at 2:00 p.m.**, at which time the Applicant and the undersigned representative will telephone Examiners Yu and Caputa at 703-308-3995.

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Remarks

Claims 1-66 are pending in this application. Claims 1 and 66 are the only independent claims pending.

Overview of Arguments

The Applicant believes that most of the Examiner's claim rejections are premised on an inaccurate understanding of the invention. The Examiner appears to believe that the claimed methods are simply a conglomeration of known anti-tumor methods. This is incorrect.

Even though each of the agents recited in the claims was discovered by others and the activity of those individual agents is well known, the Applicant's invention involves a method of using those known agents in a synergistic way. Specifically, administration of the particular agents (and types of agents) recited in the claims induces the patient's own immune system to mount a type 1 inflammatory response against the patient's tumor. It is immaterial what, if any, anti-tumor effect may be attributable to each agent recited in the claims when the agent is used alone, because it is the patient's immune system that kills the tumor cells. Administration of the recited agents induces the patient's anti-tumor immune response. This is why the applicants claim a method of inducing tumor cell death by administering the recited agents to the patient. The Examiner is strongly urged to consider to consider this overview when examining the claimed invention as a whole.

Each of the Examiner's objections or rejections is addressed below in the order they were presented in Paper No. 22.

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Rejection Pursuant to 35 U.S.C. § 112, First Paragraph

Claims 2 and 4-6 stand rejected pursuant to 35 U.S.C. § 112, first paragraph. In the Examiner's view, the claimed methods involve use of proteases to induce death of tumor cells. The Examiner asserts that proteases would not be expected to kill tumor cells.

The Applicant respectfully contends that the Examiner misunderstands the role of one or more proteases in the claimed methods. As recited in the rejected claims, proteases are but one example of "antigen-releasing agents" disclosed in the specification. As indicated in the specification at page 10, lines 9-17, the role of an antigen-releasing agent in the claimed methods is simply to induce release of protein fragments or other antigens from the surface of tumor cells. The specification discloses (e.g., at page 12, lines 25 and 26) that antigen-releasing agents can, but need not, also kill tumor cells. Induction of tumor cell antigen release is thought to contribute to leukocyte recruitment and activation and enhancing the type 1 inflammatory response that is induced by performing the entire method that is recited in the claims.

Examining the rejected claims as a whole, the Examiner will understand that it is immaterial whether a protease will induce tumor cell death, so long as the other portions of the claimed method are performed (see the foregoing Overview). For these reasons, the Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 2 and 4-6 pursuant to 35 U.S.C. § 112, first paragraph.

Rejection Pursuant to 35 U.S.C. § 112, Second Paragraph

Claims 2, 11, and 12 stand rejected pursuant to 35 U.S.C. § 112, second paragraph.

The Examiner questions the meaning of the term "tumor de-bulking agent" in claim 2, and suggests that a proper interpretation of this term is as a synonym of protease. The Applicant respectfully contends that this interpretation is not accurate. A

better appreciation of the term can be obtained by reviewing the paragraph that bridges pages 12 and 13 of the specification. Simply put, a "tumor de-bulking agent" is any antigen-releasing agent that exhibits significant tumor cell cytotoxicity. For example, simple proteases can clip antigens from cells, but will not necessarily kill any tumor cells. By contrast, other antigen-releasing agents, such as strong acids (e.g., a small volume of 10N HCl locally injected into a tumor mass) will induce release of antigens from tumor cells and will also kill tumor cells which it contacts. Thus, concentrated HCl is both an antigen-releasing agent and a tumor-debulking agent. The Applicant respectfully contends that a skilled artisan is aware of a wide variety of antigen-releasing agents that are available in the art, and is also aware of which of those antigen-releasing agents would also be considered tumor de-bulking agents. The Applicant requests that the Examiner reconsider and withdraw the rejection of claim 2 pursuant to 35 U.S.C. § 112, second paragraph.

The Examiner objects to the terms "concentrated hydrochloric acid" and "concentrated sulfuric acid' in claim 11 and the terms "concentrated sodium hydroxide" and "concentrated potassium hydroxide" in claim 12. The Examiner suggests that it is necessary to define how concentrated is "concentrated." The Applicant respectfully replies that the term "concentrated" used with strong acids and bases is a convention in the chemical and pharmaceutical fields and that it is not either possible or necessary to place an explicit limit on how "concentrated" a strong acid or a strong base must be in order to be referred to as a concentrated acid or base. The skilled artisan is able to determine the concentration of a strong acid or base that is necessary to cause antigen release simply by referring to the literature (e.g., information regarding safety or toxicity for the selected acid or base). For this reason, the Applicant respectfully contends that a skilled artisan would have no difficulty interpreting the terms "concentrated" strong acid

or "concentrated" strong base, and that the Examiner's rejection of claims 11 and 12 pursuant to 35 U.S.C. § 112, second paragraph should be withdrawn.

Rejection Pursuant to 35 U.S.C. § 103(a) Over Lee in View of Tannenbaum or Lanni

Before addressing the merits of the obviousness rejections, the Applicant reminds the Examiner that potential obviousness of the claimed methods must be performed by analyzing the claimed methods "as a whole." MPEP §2141.02. The Applicant respectfully contends that the Examiner's obviousness-type rejections amount to nothing more than a hindsight-based conglomeration of non-related prior art. There is no basis in the prior art cited by the Examiner for combining the recited references in the manner suggested by the Examiner and no expectation that the synergistic effects produced by the claimed methods would be obtained, based only on the cited art.

The Examiner rejects claims 1, 3, 13-17, 19, 20, 25-29, and 31-39 pursuant to 35 USC 103(a) over Lee in view of either Lanni or Tannenbaum. The Examiner contends that Lee teaches using

i) anti-Fas antibody as an antigen-releasing agent,
ii) TNF, and
iii) IFN-gamma

to induce tumor cell death. The Examiner contends that Tannenbaum teaches that some of the cytokines claimed as leukocyte attractants have anti-tumor activity. The Examiner finally contends that Lanni teaches using combinations of anti-tumor agents. The Examiner is requested to review the foregoing Overview if she has not already done so, and to consider the following comments in the context of examination of the claimed methods as a whole (i.e., as a method that induces an anti-tumor type 1 inflammatory response in a tumor).

There are serious shortcomings to all of the examiner's contentions regarding obviousness of the claimed methods. For example, Lee teaches that a Fas-

binding antibody can be used to induce apoptosis of Fas-expressing tumor cells in vitro, but only in the presence of added TNF and IFN-gamma. When the antibody was administered to mice into which syngeneic Fas-expressing tumor cells had been added, neither TNF nor IFN-gamma was administered. To the extent that either TNF or IFN-gamma was considered necessary for activity attributable to anti-Fas antibodies *in vivo*, normal bodily levels of TNF and IFN-gamma were relied upon. Therefore, Lee does not teach administering "an antigen-releasing agent" to an animal in conjunction with administration of IFN-gamma and a second IR1-promoting agent, as claimed.

Lee also does not teach administering a leukocyte attractant. The Examiner purports to combine Lee with at least Tannenbaum. Tannenbaum teaches that IL-12 is a leukocyte attractant and exhibits anti-tumor activity. Tannenbaum also teaches that Mig and IP-10 enhance the anti-tumor and leukocyte-attractant effects of IL-12 and that expression of Mig and IP-10 is enhanced by IFN-gamma. Assuming that IL-12 is used in the claimed method as the leukocyte attractant and that Tannenbaum can be read to teach using IL-12 and IFN-gamma together, Lee does not teach administering

i) an antigen-releasing agent and
ii) a second IR1-promoting agent.

Alternatively, if IL-12 is used as the second IR1-promoting agent in the claimed method, then Lee does not teach administering

i) an antigen-releasing agent or
ii) a leukocyte attractant.

Furthermore, all of Tannenbaum's data are in mice, and their results are not reliably transferable to humans. The Examiner's assertion that similar effects would be obtained in humans is no more than a guess.

Even if all of the elements of the claimed method were present in Lee and Tannenbaum, there is no motivation to combine these two references. The Examiner's contention is, in essence, that skilled artisans know that you can combine anti-tumor treatments. As a matter of law, that is not sufficient. The Examiner must show where and how information in the cited references would motivate a skilled artisan to combine

the cited references. The Examiner has not done that, and must withdraw the obviousness rejection over Lee and Tannenbaum for that reason as well.

The Examiner purports that Lanni teaches use of combinations of anti-tumor treatments. However, Lanni simply teaches that paclitaxel can enhance expression of TNF-alpha, and that at least some of the anti-tumor effect of paclitaxel may be attributable to the TNF-alpha-expression-enhancing effect of paclitaxel (i.e., combined with known anti-tumor properties of TNF-alpha). The Examiner's reference to Figure 3 is curious, since there seems to be only one anti-tumor agent (paclitaxel) that is administered in the experiment corresponding to the figure.

As noted above, Lee does not teach administering an antigen-releasing agent to an animal in conjunction with administration of IFN-gamma and a second IR1-promoting agent, as claimed. Lanni also does not teach administering an antigen-releasing agent to an animal. Furthermore, Lanni does not teach administering a leukocyte attractant to a tumor (locally or otherwise). Thus, even when combined, Lee and Lanni fail to teach every element recited in the claims.

As with the Lee and Tannenbaum references, there is not motivation within either the Lee reference or the Lanni reference to combine one with the other. There is also no motivation among the Lee, Tannenbaum, and Lanni references to combine all three references. Furthermore, there is no teaching in these references that indicates that combination of their disclosures would yield a method of inducing an anti-tumor type 1 inflammatory response in a tumor.

For the foregoing reasons, the Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1, 3, 13-17, 19, 20, 25-29, and 31-39 pursuant to 35 USC 103(a) over Lee in view of either Lanni or Tannenbaum.

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Rejection Pursuant to 35 U.S.C. § 103(a) Over Lee in View of Tannenbaum or Lanni and Further in View of Other References

The remainder of the Examiner's 35 U.S.C. § 103(a) rejections (relating to claims 7-12, 17, 18, 30, and 40-66) rely on Lee + (Tannenbaum or Lanni) + (another reference). None of the other reference corrects the deficiencies of the Lee, Tannenbaum, and Lanni references, and the Examiner's rejection of these claims is improper for the same reasons referenced above. There is no motivation to combine any of these references, and no expectation that an anti-tumor type 1 inflammatory response would be induced even if the cited references were combined. Reconsideration and withdrawal of the Examiner's rejection of claims 7-12, 17, 18, 30, and 40-66 pursuant to 35 U.S.C. § 103(a) are requested for that reason.

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U.S. Patent Application Ser. No. 09/756,978
Response Filed in
Response to Office Action Dated 11 April 2003

ATTORNEY DOCKET NO: E0631-00001

Summary

For the reasons set forth above, the Applicant respectfully contends that each of claims 1-66 would be in condition for allowance upon formal entry of this Draft Amendment, with claims 1 and 66 either as previously amended (i.e., currently pending) or as amended in the manner proposed herein. The Examiner is requested to discuss these issues with the Applicant and the undersigned representative during the telephone interview scheduled for **29 July 2003 at 2:00 p.m.**

Respectfully submitted,

Eugene Roussel

_____ By: _____
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Enclosures: Petition for a One-Month Extension of Time (Not included with Draft)